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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
00537-191WO1		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/17401	23/06/2000	25/06/1999
International Patent Classification (IPC) or national classification and IPC C07K14/655		
Applicant SOCIETE DE CONSEILS DE RECHERCHES ET D'APPL..et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supcrting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25/01/2001	26.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Rojo Romeo, E Telephone No. +49 89 2399 7321

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/17401

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-17 as originally filed

Claims, No.:

1-11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-11 (partially).

because:

☒ the said international application, or the said claims Nos. 1-11 (partially) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-11 (partially).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	6-11 (see separate sheet)

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

R Item I

Basis of this report

Since the Applicant failed to reply to the Written Opinion, the present IPER is based on said Written Opinion.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The present set of claims is directed to an extremely large number of possible compounds. Consequently, the entire scope of claim 1 cannot be construed without an immense burden of work and the examination is limited to the two compounds given in the examples.
any other subject-matter is therefore, disregarded.

Re Item IV

Lack of unity of invention

The present application concerns cyclic peptides having a somatostatin agonist activity. The common inventive concept linking the present set of claims is the general formula I, i.e. substituted cyclic peptides having somatostatin agonist activity. As mentioned in the present application (see e.g. page 4) and in prior art (see D3-D6), cyclic hexa- and octa-peptides have been synthesized which possess the whole spectrum of effects of somatostatin. Moreover, some of the specific claimed compounds are disclosed in e.g. D1. In view of the prior art, the common concept linking the claimed compounds is not inventive and the problem of the present application can be redefined as the provision of additional peptides having somatostatin activity.
Consequently, each and every single compound may be considered, in the regional phase as an independent invention.

The Applicant's attention is drawn to the fact that each of the two claimed compounds may be considered to define an independent invention in the regional phase.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following comments are made as far as the claims concern the two compounds for which the synthesis is described in the examples and which are claimed in claim 4.

Reference is made to the following documents cited in the International Search Report:

D1: WO 98 24807 A (BIOMEASURE INC ;MORGAN BARRY (US); MURPHY WILLIAM (US); ADMINISTRA) 11 June 1998 (1998-06-11)

D2: EP-A-0 505 680 (BIOSIGNAL KUTATO FEJLESZTOE) 30 September 1992 (1992-09-30)

D3: WO 98 50063 A (CEDARS SINAI MEDICAL CENTER ;MELMED SHLOMO (US); SHIMON ILAN (US);) 12 November 1998 (1998-11-12)

D4: WO 98 51332 A (SOD CONSEILS RECH APPLIC ;CAWTHORNE MICHAEL ANTHONY (GB); SENNITT) 19 November 1998 (1998-11-19)

D5: WO 98 51330 A (SOD CONSEILS RECH APPLIC ;CAWTHORNE MICHAEL ANTHONY (GB); SENNITT) 19 November 1998 (1998-11-19)

D6: WO 98 51331 A (SOD CONSEILS RECH APPLIC ;CAWTHORNE MICHAEL ANTHONY (GB); SENNITT) 19 November 1998 (1998-11-19)

1. Novelty (Art. 33(2) PCT)

None of the documents cited in the International Search Report discloses the claimed subject-matter. The current set of claims is thus considered novel over these documents as far as they concern the two compounds mentioned above.

The Applicant's attention is drawn to the fact that many of the compounds claimed in D1 fall under the scope of claim 1. Thus the broad claim as it stands would not be novel over prior art.

2. Inventive step (Art. 33(3) PCT)

D1 or D2 can be considered as closest prior art since these documents disclose somatostatin homologs. The problem underlying the present application is the provision of somatostatin homologs with somatostatin agonist activity. The solution provided by the present application is the provision of the two compounds of claim 4. There was no hint in the prior art for the synthesis of these specific two compounds and that these compounds may have somatostatin agonist activity. Thus, inventive activity could be acknowledged for these two specific compounds, given that the data can be provided that these compounds indeed have the claimed technical effects (i.e. somatostatin agonist). Moreover, as mentioned at page 1 of the present application somatostatin analogs (i.e. having agonist activity) were also known from prior art. The present application fails to show that the two claimed compounds have a technical

advantage over the somatostatin analogs already known (see D3-D6). In the absence of such data, inventive activity cannot be acknowledged for the present set of claims.
In addition, the Applicant's attention is drawn to the fact that the use of somatostatin analogs having a Tyr at position A1 for imaging was known from prior art (see e.g. D1, page 24). Consequently, the skilled person would use any other somatostatin analog having this technical characteristic for this purpose. Thus claims 10 and 11 lack inventive activity.

Consequently, claims 1-11 lack inventive step.

3. Industrial applicability (Art. 33(4) PCT)
For the assessment of the present claims 6-11 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

1. Clarity (Art. 6 PCT)

1.1 The Applicant's attention is drawn to the fact that the intention of use does not limit the scope of a claim which is directed to a composition. The claim must be interpreted as being directed to a composition per se regardless of its use. No unified criteria exist in the PCT as far as first medical use is concerned. The EPO, for instance, will allow claims in a form such as:"substance or composition X", followed by the indication of use ("for use as a medicament"). Thus, claim 5 is read as being directed to a composition comprising either of the two claimed peptides.

1.2 Concerning claims 5-7, in the absence of data concerning the use of the claimed compounds, the term "effective amount" is unclear.

2. Support by specification (Art. 6 PCT), in combination with Art. 5 PCT (complete and

enabling disclosure)

2.1 No data is provided concerning the activity of the two claimed compounds (somatostatin agonist activity, selective binding to somatostatin subtype receptor type 5). Thus, the assumption that these compounds have somatostatin agonist activity is speculative. Concerning this, it is noteworthy to mention that the present specification recommends to test the claimed compounds for agonist or antagonist activity (see page 13)! An objection for lack of support thus arises.

2.1 Similarly, the uses of the two claimed compounds in medical treatment are based on speculations derived from the uses of somatostatin itself but without any experimental proof and are therefore also the subject of an objection for lack of support by the specification (claims 6-9).

JRG
YAT

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
TSAO, Y., Rocky
Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
ETATS-UNIS D'AMERIQUE

RECEIVED
JAN 16 2001
FISH & RICHARDSON, P.C.
BOSTON OFFICE

Date of mailing (day/month/year)	
04 January 2001 (04.01.01)	
Applicant's or agent's file reference 00637-191WO1	**IMPORTANT NOTICE**
International application No. PCT/US00/17401	**International filing date** (day/month/year) 23 June 2000 (23.06.00) — **Priority date** (day/month/year) 25 June 1999 (25.06.99)
Applicant SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES S.A.S. et al	

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AG,AU,BZ,DZ,KP,KR,MZ,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   04 January 2001 (04.01.01) under No. WO 01/00676

No Document Required *
Reviewed By Practice Systems
Initials: CDB
Reviewed By Billing Secretary
Initials:

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the **applicant's sole responsibility** to monitor the 19-month time limit.

Note that **only an applicant** who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

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(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 60/141,028 (CIP)
Filed on 25 June 1999 (25.06.1999)

(71) Applicant *(for all designated States except US)*: SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES S.A.S. [FR/FR]; 51, 53 rue du Docteur Blanche, F-75016 Paris (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: MORGAN, Barry, A. [US/US]; 237 Prospect Street, Franklin, MA 02038 (US). SADAT-AALAEE, Dean [US/US]; 37 Brookdale Circle, Shrewsbury, MA 01545 (US).

(74) Agent: TSAO, Y., Rocky; Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110-2804 (US).

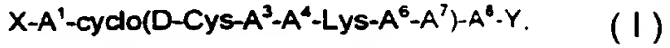
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

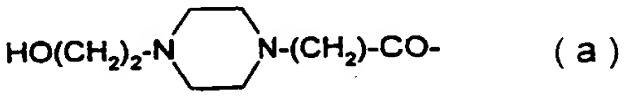
Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

[Continued on next page]

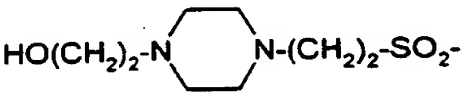
(54) Title: SOMATOSTATIN AGONISTS



(I)



(a)



(b)

(57) Abstract: The present invention is directed to cyclic peptides of formula (I): X-A[1]-cyclo(D-Cys-A[3]-A[4]-Lys-A[6]-A[7])-A[8]-Y, or a pharmaceutically acceptable salt thereof, wherein X is H, formula (a) or formula (b); A[1] and A[3] are each independently the D- or L-isomer of an amino acid selected from the group consisting of Phe, Tyr, Tyr(I), Trp, 3-Pal, 4-Pal, Cpa and Nal; A[4] is L-Trp, D-Trp, L-β-methyl-Trp or D-β-methyl-Trp; A[6] is -NH-(CHR[1])$_n$-CO-, where n is 2, 3, or 4; A[7] is L- or D-Cys; A[8] is the D- or L-isomer of an amino acid selected from the group consisting of Phe, Tyr, Tyr(I), Trp, Nal, Cpa, Val Leu, Ile, Ser and Thr; Y is NR[2]R[3] where R[2] and R[3] are each independently H or (C_1-C_5)alkyl; R[1] is selected from the group consisting H, (C_1-C_4)alkyl and -CH_2-aryl; wherein said aryl is an optionally substituted moiety selected from the group consisting of phenyl, 1-naphthyl, and 2-naphthyl, wherein said optionally substituted moiety is optionally substituted with one or more substituents each independently selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, aryl, aryl(C_{1-6})alkyl, (C_{1-6})alkoxy, -N(R[4]R[5]), -COOH, -CON(R[4]R[5]), halo, -OH, -CN, and -NO_2; R[4] and R[5] each is, independently for each occurrence, H or (C_{1-3})alkyl; where the Cys of A[2] is bonded to the Cys of A[7] by a di-sulfide bond formed from the thiol groups of each Cys; pharmaceutical compositions comprising said peptides and the use thereof as a somatostatin receptor subtypes agonist. The peptides of the present invention bind selectively to the somatostatin subtype receptor type-5 and elicit an agonist effect from the somatostatin subtype receptors that the peptides bind to.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

SOMATOSTATIN AGONISTS

Background of the Invention

The present invention is directed to cyclic peptides that have somatostatin agonist activity, as defined by formula (I), shown and defined hereinbelow, or a pharmaceutically acceptable salt thereof, pharmaceutical compositions comprising said peptides and the use thereof as a somatostatin receptor subtypes agonist. The peptides of the present invention bind selectively to the somatostatin subtype receptor 5 and elicit an agonist effect from the somatostatin subtype receptors that the peptides bind to.

Somatostatin (SRIF) is a cyclic tetradecapeptide hormone containing a disulfide bridge between position 3 and position 14 (Heiman, et al., Neuroendocrinology, 45:429-436 (1987)) and has the properties of inhibiting the release of growth hormone (GH) and thyroid-stimulating hormone (TSH), inhibiting the release of amylin, insulin and glucagon, reducing gastric secretion and neurotransmitter release. Metabolism of somatostatin by aminopeptidases and carboxypeptidases leads to a short duration of action. Because of the short half-life of the native somatostatin, various somatostatin analogs have been developed, e.g., for the treatment of acromegaly. Raynor, et al., Molecular Pharmacol. 43:838 (1993).

Five distinct somatostatin receptors have been identified and characterized. Hoyer, et al., Naunyn-Schmiedeberg's Arch. Pharmacol., 350:441 (1994). Somatostatin binds to five distinct receptor (SSTR) subtypes with relatively high and equal affinity for each subtype. Binding to the different types of somatostatin subtypes have been associated with the treatment of the following conditions and/or diseases. ("SSTR-2") (Raynor, et al., Molecular Pharmacol. 43:838 (1993); Lloyd, et al., Am. J. Physiol. 268:G102 (1995)) while the inhibition of insulin has been attributed to the somatostatin type-5 receptor ("SSTR-5") (Coy, et al. 197:366-371 (1993)). Activation of types 2 and 5 have been associated with growth hormone suppression and more particularly GH secreting adenomas (Acromegaly) and TSH secreting adenomas. Activation of type 2 but not type 5 has been associated with treating prolactin secreting adenomas. Other indications associated with activation

of the somatostatin subtypes are inhibition of insulin and/or glucagon and more particularly diabetes mellitus, angiopathy, proliferative retinopathy, dawn phenomenon and Nephropathy; inhibition of gastric acid secretion and more particularly peptic ulcers, enterocutaneous and pancreaticocutaneous fistula, irritable bowel syndrome, Dumping syndrome, watery diarrhea syndrome, AIDS related diarrhea, chemotherapy-induced diarrhea, acute or chronic pancreatitis and gastrointestinal hormone secreting tumors; treatment of cancer such as hepatoma; inhibition of angiogenesis, treatment of inflammatory disorders such as arthritis; retinopathy; chronic allograft rejection; angioplasty; preventing graft vessel and gastrointestinal bleeding. It is preferred to have an analog which is selective for the specific somatostatin receptor subtype responsible for the desired biological response, thus, reducing interaction with other receptor subtypes which could lead to undesirable side effects.

The peptides of formula (I) are a sub-genus encompassed by a genus of compounds described and claimed in copending U.S. Application No. 08/855,204, filed May 13, 1997, which application is assigned in part to the assignee of the present invention. The compounds of formula (I) of the present application are not specifically described in U.S. Application No. 08/855,204. It has been unexpectedly and surprisingly discovered that the compounds of formula (I) of the present invention possess somatostatin agonist activity. This is an unexpected and surprising discovery since the compounds of U.S. Application No. 08/855,204 were originally found to possess somatostatin antagonist activity.

Summary of the Invention

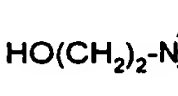
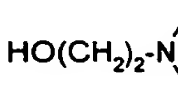
In one aspect, the present invention is directed to a peptide of the formula (I),

$$X\text{-}A^1\text{-cyclo(D-Cys-}A^3\text{-}A^4\text{-Lys-}A^6\text{-}A^7\text{)-}A^8\text{-Y},$$

(I)

or a pharmaceutically acceptable salt thereof,

wherein

X is H,  or  ;

A^1 and A^3 are each independently the D- or L-isomer of an amino acid selected from the group consisting of Phe, Tyr, Tyr(I), Trp, 3-Pal, 4-Pal, Cpa and Nal;

A^4 is L-Trp, D-Trp, L-ß-methyl-Trp or D-ß-methyl-Trp;

A^6 is -NH-$(CHR^1)_n$-CO-, where n is 2, 3, or 4;

A^7 is L- or D-Cys;

A^8 is the D- or L-isomer of an amino acid selected from the group consisting of Phe, Tyr, Tyr(I), Trp, Nal, Cpa, Val, Leu, Ile, Ser and Thr;

Y is NR^2R^3 where R^2 and R^3 are each independently H or $(C_1$-$C_5)$alkyl;

R^1 is selected from the group consisting H, $(C_1$-$C_4)$alkyl and -CH_2-aryl; wherein said aryl is an optionally substituted moiety selected from the group consisting of phenyl, 1-naphthyl, and 2-naphthyl, wherein said optionally substituted moiety is optionally substituted with one or more substituents each independently selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, aryl, aryl(C_{1-6})alkyl, (C_{1-6})alkoxy, -$N(R^4R^5)$, -COOH, -$CON(R^4R^5)$, halo, -OH, -CN, and -NO_2;

R^4 and R^5 each is, independently for each occurrence, H or (C_{1-3})alkyl;

where the Cys of A^2 is bonded to the Cys of A^7 by a di-sulfide bond formed from the thiol groups of each Cys.

A preferred group of peptides of the foregoing peptide of formula (I) is wherein

X is H;

A^1 is L-Phe, D-Phe, L-Cpa or D-Cpa;

A^3 is L-Tyr, L-Trp or L-3-Pal;

A^4 is D-Trp;

A^6 is β-Ala or Gaba;

A^7 is L-Cys;

A^8 is Thr, L-Trp, L-Leu or L-Nal; and

R^2 and R^3 are each H; or a pharmaceutically acceptable salt thereof.

Preferred peptides of the immediately foregoing group of peptides are:

Cpa-cyclo(D-Cys-3-Pal-D-Trp-Lys-Gaba-Cys)-Nal-NH_2;

Cpa-cyclo(D-Cys-3-Pal-D-Trp-Lys-β-Ala-Cys)-Nal-NH_2;

Phe-cyclo(D-Cys-3-Pal-D-Trp-Lys-Gaba-Cys)-Nal-NH_2;

Phe-cyclo(D-Cys-Tyr-D-Trp-Lys-Gaba-Cys)-Nal-NH_2;

Ph -cyclo(D-Cys-Trp-D-Trp-Lys-Gaba-Cys)-Nal-NH_2;
Phe-cyclo(D-Cys-Tyr-D-Trp-Lys-Gaba-Cys)-Trp-NH_2;
D-Phe-cyclo(D-Cys-Tyr-D-Trp-Lys-Gaba-Cys)-Nal-NH_2;
D-Phe-cyclo(D-Cys-Tyr-D-Trp-Lys-Gaba-Cys)-Leu-NH_2; and
Phe-cyclo-(D-Cys-Tyr-D-Trp-Lys-Gaba-Cys)-Thr-NH_2; or a pharmaceutically acceptable salt thereof.

Preferred peptides of the immediately foregoing group of peptides are:
Cpa-cyclo(D-Cys-3-Pal-D-Trp-Lys-Gaba-Cys)-Nal-NH_2; and
Cpa-cyclo(D-Cys-3-Pal-D-Trp-Lys-β-Ala-Cys)-Nal-NH_2; or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a pharmaceutical composition useful for eliciting a somatostatin agonist response in a human or other animal which comprises an effective amount of a peptide of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another aspect, the present invention provides a method of eliciting a somatostatin agonist response in a human or other animal in need thereof, which comprises administering an effective amount of a peptide of formula (I) or a pharmaceutically acceptable salt thereof to the human or other animal.

In a further aspect, the present invention provides a method of selectively binding a somatostatin subtype receptor type 5 in a human or other animal, which comprises administering an effective amount of a peptide of formula (I) or a pharmaceutically acceptable salt thereof to the human or other animal.

In still a further aspect, the present invention provides a method of treating a disease or condition in a human or other animal in need thereof, which comprises administering an effective amount of a peptide of formula (I) or a pharmaceutically acceptable salt thereof to the human or other animal, wherein said disease or condition is selected from the group consisting of Cushings Syndrome, gonadotropinoma, hyperparathyroidism, Paget's disease, VIPoma, nesidioblastosis, hyperinsulinism, gastrinoma, Zollinger-Ellison Syndrome, hypersecretory diarrhea related to AIDS and other conditions, irritable bowel syndrome, pancreatitis, Crohn's Disease, systemic sclerosis, thyroid cancer, psoriasis, hypotension, panic

attacks, sclerodoma, small bowel obstruction, gastroesophageal reflux, duodenogastric reflux, Graves' Disease, polycystic ovary disease, upper gastrointestinal bleeding, pancreatic pseudocysts, pancreatic ascites, leukemia, meningioma, cancer cachexia, acromegaly, restenosis, hepatoma, lung cancer, melanoma, inhibiting the accelerated growth of a solid tumor, decreasing body weight, treating insulin resistance, Syndrome X; prolonging the survival of pancreatic cells, fibrosis, hyperlipidemia, hyperamylinemia, hyperprolactinemia and prolactinemia.

In still a further aspect , the present invention provides a method of inhibiting the secretion of growth hormone, insulin, glucagon or pancreatic exocrine secretion in a human or other animal in need thereof, which comprises administering a peptide of formula (I) or a pharmaceutically acceptable salt thereof to said human or other animal.

In an even further aspect, the present invention provides a method of imaging cells containing somatostatin receptors *in vivo* in a human or other animal, which comprises administering a peptide of formula (I), provided that at least one of A^1, A^3 or A^8 is Tyr(I), or a pharmaceutically acceptable salt thereof to said human or other animal.

In another aspect, the present invention provides a method of imaging cells containing somatostatin receptors *in vitro*, which comprises administering a peptide of formula (I), provided that at least one of A^1, A^3 or A^8 is Tyr(I), or a pharmaceutically acceptable salt thereof to said human or other animal. Such peptides of the present invention can be used either *in vivo* to detect cells having somatostatin receptors (e.g., cancer cells) or *in vitro* as a radioligand in a somatostatin receptor binding assay.

The three letter abbreviations accepted in the art are used to refer to the amino acids in a peptide of the present invention. In the formula set forth herein, the disulfide bond between the thiol group on the side chain of residue A_2 (i.e., D-Cys) and the thiol group on the side chain of residue A_7 (i.e., L-Cys or D-Cys) is not shown. The following amino acid abbreviations stand for the name indicated next to it: Cpa = p-chlorophenylalanine; Nal = β-(2-naphthyl)alanine; 3-Pal = β-(3-pyridyl)-alanine; 4-Pal = β-(4-pyridyl)-alanine; and Gaba = 4-aminobutyric acid. The

definition of "-NH-$(CH_2)_n$-CO- where n is 2, 3, or 4" encompasses such amino acids as β-Ala and Gaba.

Unless noted otherwise, the three letter abbreviation of an amino acid refers to the L-isomer.

The term alkyl is intended to include those alkyl groups of the designated length in either a straight or branched configuration. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, and the like. When the term C_0-alkyl is included in a definition it is intended to denote a single covalent bond.

The term alkenyl is intended to include hydrocarbon groups having one or more double bonds and the designated number of carbon atoms in either a straight or branched configuration. Exemplary of such alkenyl groups are ethenyl, propenyl, isopropenyl, butenyl, sec-butenyl, tertiary butenyl, pentenyl, isopentenyl, hexenyl, isohexenyl and the like.

The term alkynyl is intended to include those alkynyl groups, i.e., hydrocarbon groups having one or more triple bonds, having the designated number of carbon atoms in either a straight or branched configuration. Exemplary of such alkynyl groups are ethynyl, propynyl, butynyl, pentynyl, isopentynyl, hexynyl, isohexynyl and the like.

The term alkoxy is intended to include those alkoxy groups having the designated number of carbon atoms in either a straight or branched configuration. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

The term aryl is intended to include aromatic rings known in the art, which can be mono-cyclic or bi-cyclic, such as phenyl and naphthyl.

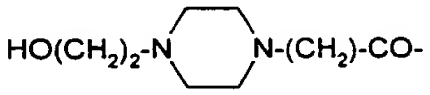
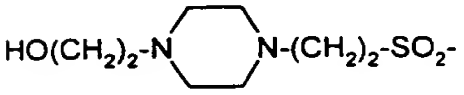
The term halo is intended to include chlorine, bromine, iodine, and fluorine.

Detailed Description

One skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. The following specific embodiments are, therefore, to be construed as merely illustrations of the invention and is not meant to be construed as limiting the full scope of the invention.

Peptides of the present invention can be and were synthesized on Rink Amide MBHA resin, (4-(2',4'-dimethoxyphenyl-Fmoc-aminomethyl)-phenoxyacetamido-norleucyl-MBHA resin), using a standard solid phase protocol for FMOC chemistry and cleaved from the resin with a TFA/Phenol/H_2O/triisopropylsilane (83ml/5g/10ml/2ml) mixture. Peptides were cyclized in CH_3CN/H_2O (5ml/5ml) using EKATHIOX™ resin (EKAGEN Corporation, San Carlos, CA) and purified on C_{18} silica (Rainin Instruments Co., Woburn, MA now Varian Analytical, Walnut Creek, CA), using acetonitrile/0.1% trifluoroacetic acid buffers. Homogeneity was assessed by analytical HPLC and were determined to be >95% for each peptide. Peptides were characterized by mass spectrometry.

The synthesis of iodinated Tyr (Tyr(I)) peptides of formula (I) of the present invention (e.g., the chloramine-T method) is well documented and are within the ability of a person of ordinary skill in the art. See, e.g., Czernick, et al., J. Biol. Chem. 258:5525 (1993) and European Patent No. 389,180 B1.

A peptide of formula (I) wherein X is  or  , can be synthesized according to the processes and teachings of U.S. Patent No. 5,552,520, the contents of which are incorporated herein in its entirety.

Below is a detailed description of the synthesis of Examples 1 and 2. Other peptides within a compound of formula (I) can be prepared by making appropriate modifications, well-known to one of ordinary skill in the art of peptide synthesis.

EXAMPLE 1

Step 1 = Preparation of Fmoc-Cpa-S-trityl-D-Cys-Pal-N-in-t-Boc-D-Trp-N-ε-t-Boc-Lys-β-Ala-S-trityl-Cys-Nal-4-(2',4'-Dimethoxyphenylamino methyl) phenoxy-acetamido-norleucyl-4-methylbenzhydrylamine resin.

Rink amide MBHA resin (Novabiochem, Inc., San Diego, CA) 0.5g, (0.265 mmole), was placed in a reaction vessel of a 24-RV peptide synthesizer, assembled

by connecting a shaker (from the Burrell Wrist-Action Laboratory Shaker), a solvent distributor and a vacuum pump. The peptide synthesizer was programmed to perform the following reaction cycle:

a. Dimethylformamide;

b. 25% piperidine in dimethylformamide (manually added) (2 times for 15 minutes each with 1 time wash with DMF in between);

c. DMF washes (3 x 10 mL, 1 minute each);

The resin was stirred with FMOC-Nal (1.06 mmol), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBUT) 1.007 mmole), and diisopropylethyl amine (2.12 mmole) in dimethylformamide for about 1½ hours and the resulting amino acid resin was then cycled through steps (a) to (c) in the above washing/deblocking program.

The following amino acids were coupled successively to the Nal-resin by the same procedure: Fmoc-S-Trityl-Cys, Fmoc-β-Ala, N-ε-t-Boc-Lys, Fmoc-(N-in-t-Boc)-D-Trp, Fmoc-Pal, Fmoc-S-trityl-D-Cys, and Fmoc-p-Cl-Phe.

After washing with DMF (3 x 10 mL, about 1 minute each) and drying under vacuum, the complete peptide resin weighed 0.749 g.

Step 2: Preparation of H-Cpa-cyclo(D-Cys-Pal-D-Trp-Lys-β-Ala-Cys)-Nal-NH_2

The peptide resin obtained from Step 1 of Example 1 (0.36 g, 0.087 mmole) was mixed with a freshly prepared solution of TFA (8.8 mL), phenol (0.5g), H_2O (0.5 mL) and triisopropylsilane (0.2 mL) at room temperature and stirred for about 2½ hours. Excess TFA was evaporated under reduced pressure to yield an oily residue. Ether was then added to the oily residue and the free linear peptide was precipitated, filtered, and washed with dry ether. The crude peptide was then dissolved in 10 mL of CH_3CN/H_2O (5 mL/5 mL), followed by the addition of 200 mg EKATHIOX™ resin. The mixture was stirred overnight and filtered. The filtrate was evaporated to a small volume then applied to a column (22-250 mm) of microsorb octadecylsilane silica (5 µm). Elution with a linear gradient (20% to 40%, over 60 minutes) of acetonitrile in water, (both solvents have 0.1% trifluoroacetic acid) yields fractions which were examined by analytical high performance liquid

chromatography ('HPLC") and pooled to give maximum purity. Lyophilization of the solution from water gave 26 mg of the product as white, fluffy powder. The product was found to be homogeneous by HPLC C_{18} silica using the same eluant as described above and a linear gradient (30% to 70%, over 15 min) (Retention Time - 6.313 minutes). Infusion mass spectrometry confirmed the composition of the cyclic octapeptide, MW 1133.8.

EXAMPLE 2

Step 1: Preparation of Fmoc-Cpa-S-trityl-D-Cys-Pal-in-t-Boc-D-Trp-N-ε-t-Boc-Lys-Gaba-S-trityl-Cys-Nal-4-(2',4'-Dimethoxyphenylaminomethyl) Phenoxyacetamido-norleucyl-4-methylbenzhydrylamine resin

Rink amide MBHA resin (Novabiochem, Inc. San Diego, CA) 0.2 g, (0.106 mmole) was placed in reaction vessel #3, (RV-3) of the 24-RV peptide synthesizer. The peptide synthesizer was programmed to perform the following reaction cycle:

a. Dimethylformamide;

b. 25% piperidine in dimethylformamide (manually added) (2 times for 15 minutes each with 1 time wash with DMF in between);

c. DMF washes (3 x 10 mL, 1 minute each);

The resin was stirred with FMOC-Nal (0.424 mmol), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBUT) 0.403 mmole), and diisopropylethyl amino (0.848 mmole) in dimethylformamide for about 1½ hours and the resulting amino acid resin was then cycled through steps (a) to (c) in the above wash program.

The following amino acids were coupled successively to the peptide resin by the same procedure: Fmoc-S-Trityl-Cys, Fmoc-Gaba, N-ε-t-Boc-Lys, Fmoc-(N-in-t-Boc)-D-Trp, Fmoc-Pal, Fmoc-S-trityl-D-Cys, and Fmoc-Cpa. After washing with DMF (3 x 10 mL, about 1 minute each) and drying under vacuum, the complete resin weighed 0.31 g.

Step 2: Preparation of H-Cpa-cyclo(D-Cys-Pal-D-Trp-Lys-Gaba-Cys)-Nal-NH_2

The peptide resin obtained from Step 1 of Example 2 was mixed with a freshly prepared solution of TFA (8.3 mL), phenol (0.5g), H_2O (1 mL) and triisopropylsilane (0.2 mL) at room temperature and stirred for about 2½ hours.

Excess TFA was evaporated under reduced pressure to give an oily residue. Ether was then added to the oily residue and the free linear peptide was precipitated, filtered, and then washed with dry ether. The crude peptide was then dissolved in 10 mL of CH_3CN/H_2O followed by the addition of 200 mg of EKATHIOX™ resin. The mixture was stirred overnight and filtered. The filtrate was evaporated to a small volume then applied to a column (22-250 mm) of microsorb octadecylsilane silica (5 µm), and eluted with a linear gradient (20 % to100 %, over 60 minutes) of acetonitrile in water, in which both solvents have 0.1% trifluoroacetic acid. Fractions were examined by analytical high performance liquid chromatography ("HPLC") and pooled to give maximum purity. Lyophilization of the solutions from water gave 13 mg of the product as white, fluffy powder. The product was found to be homogeneous by HPLC C_{18} silica using the same eluant as described above (20% to 80%, over 15 min) (Retention time - 9.195 minutes). Infusion mass spectrometry confirmed the composition of the cyclic octapeptide, MW 1147.83.

The peptides of this invention can be provided in the form of pharmaceutically acceptable salts. Examples of such salts include, but are not limited to, those formed with organic acids (e.g., acetic, lactic, maleic, citric, malic, ascorbic, succinic, benzoic, methanesulfonic, toluenesulfonic, or pamoic acid), inorganic acids (e.g., hydrochloric acid, sulfuric acid, or phosphoric acid), and polymeric acids (e.g., tannic acid, carboxymethyl cellulose, polylactic, polyglycolic, or copolymers of polylactic-glycolic acids). A typical method of making a salt of a peptide of the present invention is well known in the art and can be accomplished by standard methods of salt exchange Accordingly, the TFA salt of a peptide of the present invention (the TFA salt results from the purification of the peptide by using preparative HPLC, eluting with TFA containing buffer solutions) can be converted into another salt, such as an acetate salt by dissolving the peptide in a small amount of 0.25 N acetic acid aqueous solution. The resulting solution is applied to a semi-prep HPLC column (Zorbax, 300 SB. C-8). The column is eluted with (1) 0.1N ammonium acetate aqueous solution for 0.5 hrs., (2) 0.25N acetic acid aqueous solution for 0.5 hrs. and (3) a linear gradient (20% to 100% of solution B over 30 min.) at a flow rate of 4 ml/min (solution A is 0.25N acetic acid aqueous solution; solution B is 0.25N acetic acid in acetonitrile/water, 80:20). The fractions containing

the peptide are collected and lyophilized to dryness.

The affinity of a peptide of the present invention for human somatostatin subtype receptors 1 to 5 (sst_1, sst_2, sst_3, sst_4 and sst_5, respectively) is determined by measuring the inhibition of (^{125}I-Tyr^{11})SRIF-14 binding to CHO-K1 transfected cells.

The human sst_1 receptor gene was cloned as a genomic fragment. A 1.5 Kb *Pst*I-X*mn*I segment containg 100 bp of the 5'-untranslated region, 1.17 Kb of the entire coding region, and 230 bp of the 3'-untranslated region was modified by the Bg1II linker addition. The resulting DNA fragment was subcloned into the *BamH*I site of a pCMV-81 to produce the mammalian expression plasmid (provided by Dr. Graeme Bell, Univ. Chicago). A clonal cell line stably expressing the sst_1 receptor was obtained by transfection into CHO-K1 cells (ATCC) using the calcium phosphate co-precipitation method (1). The plasmid pRSV-neo (ATCC) was included as a selectable marker. Clonal cell lines were selected in RPMI 1640 media containing 0.5 mg/ml of G418 (Gibco), ring cloned, and expanded into culture.

The human sst_2 somatostatin receptor gene, isolated as a 1.7Kb *Bam*HI-*Hind*III genomic DNA fragment and subcloned into the plasmid vector pGEM3Z (Promega), was kindly provided by Dr. G. Bell (Univ. of Chicago). The mammalian cell expression vector is constructed by inserting the 1.7Kb *Bam*H1-*Hind*II fragment into compatible restriction endonuclease sites in the plasmid pCMV5. A clonal cell line is obtained by transfection into CHO-K1 cells using the calcium phosphate co-precipitation method. The plasmid pRSV-neo is included as a selectable marker.

The human sst_3 was isolated at genomic fragment, and the complete coding sequence was contained within a 2.4 Kb *Bam*HI/*Hind*III fragment. The mammalian expression plasmid, pCMV-h3 was constructed by inserting the a 2.0 Kb *Nco*I-*Hind*III fragment into the EcoR1 site of the pCMV vector after modification of the ends and addition of EcoR1 linkers. A clonal cell line stably expressing the sst_3 receptor was obtained by transfection into CHO-K1 cells (ATCC) using the calcium phosphate co-precipitation method. The plasmid pRSV-neo (ATCC) was included as a selectable marker. Clonal cell lines were selected in RPMI 1640 media containing 0.5 mg/ml of G418 (Gibco), ring cloned, and expanded into culture.

The human sst_4 receptor expression plasmid, pCMV-HX was provided by Dr. Graeme Bell (Univ. Chicago). The vector contains the 1.4 Kb *Nhe*I-*Nhe*I genomic fragment encoding the human sst_4, 456 bp of the 5'-untranslated region and 200 bp of the 3'-untranslated region, clone into the *Xba*I/*Eco*R1 sites of PCMV-HX. A clonal cell line stably expressing the sst_4 receptor was obtained by transfection into CHO-K1 cells (ATCC) using the calcium phosphate co-precipitation method. The plasmid pRSV-neo (ATCC) was included as a selectable marker. Clonal cell lines were selected in RPMI 1640 media containing 0.5 mg/ml of G418 (Gibco), ring cloned, and expanded into culture.

The human sst_5 gene was obtained by PCR using a λ genomic clone as a template, and kindly provided by Dr. Graeme Bell (Univ. Chicago). The resulting 1.2 Kb PCR fragment contained 21 base pairs of the 5'-untranslated region, the full coding region, and 55 bp of the 3'-untranslated region. The clone was inserted into EcoR1 site of the plasmid pBSSK(+). The insert was recovered as a 1.2 Kb *Hind*III-*Xba*I fragment for subcloning into pCVM5 mammalian expression vector. A clonal cell line stably expressing the SST_5 receptor was obtained by transfection into CHO-K1 cells (ATCC) using the calcium phosphate co-precipitation method. The plasmid pRSV-neo (ATCC) was included as a selectable marker. Clonal cell lines were selected in RPMI 1640 media containing 0.5 mg/ml of G418 (Gibco), ring cloned, and expanded into culture.

CHO-K1 cells stably expressing one of the human sst receptor are grown in RPMI 1640 containing 10% fetal calf serum and 0.4 mg/ml geneticin. Cells are collected with 0.5 mM EDTA, and centrifuged at 500 g for about 5 min. at about 4°C. The pellet is resuspended in 50 mM Tris, pH 7.4 and centrifuged twice at 500 g for about 5 min. at about 4°C. The cells are lysed by sonication and centrifuged at 39000 g for about 10 min. at about 4°C. The pellet is resuspended in the same buffer and centrifuged at 50000 g for about 10 min. at about 4°C and membranes in resulting pellet are stored at - 80°C.

Competitive inhibition experiments of (^{125}I-Tyr^{11})SRIF-14 binding are run in duplicate in polypropylene 96 well plates. Cell membranes (10 µg protein/well) are incubated with (^{125}I-Tyr^{11})SRIF-14 (0.05 nM) for about 60 min. at about 37°C in 50 mM

HEPES (pH 7.4), 0.2% BSA, 5 mM $MgCl_2$, 200 KIU/ml Trasylol, 0.02 mg/ml bacitracin and 0.02 mg/ml phenylmethylsulphonyl fluoride.

Bound from free (^{125}I-Tyr^{11})SRIF-14 is separated by immediate filtration through GF/C glass fiber filter plate (Unifilter, Packard) presoaked with 0.1 % polyethylenimine (P.E.I.), using Filtermate 196 (Packard) cell harvester. Filters are washed with 50 mM HEPES at about 0-4°C for about 4 sec. and assayed for radioactivity using Packard Top Count.

Specific binding is obtained by subtracting nonspecific binding (determined in the presence of 0.1 µM SRIF-14) from total binding. Binding data are analyzed by computer-assisted nonlinear regression analysis (MDL) and inhibition constant (Ki) values are determined.

The determination of whether a compound of the instant invention is an agonist or an antagonist is determined by the following assay.

Functional assay: Inhibition of cAMP intracellular production:

CHO-K1 Cells expressing human somatostatin (SRIF-14) subtype receptors are seeded in 24-well tissue culture multidishes in RPMI 1640 media with 10% FCS and 0.4 mg/ml geneticin. The medium is changed the day before the experiment.

Cells at 10^5 cells/well are washed 2 times by 0.5 ml and fresh RPMI with 0.2% BSA supplemented with 0.5 mM (1) 3-isobutyl-1-methylxanthine (IBMX) and incubated for about 5 min at about 37°C.

- Cyclic AMP production is stimulated by the addition of 1mM forskolin (FSK) for about 15-30 minutes at about 37°C.
- The agonist effect of a compound is measured by the simultaneous addition of FSK (1µM) , SRIF-14 (10^{-12} M to 10^{-6} M) and a test compound (10^{-10} M to 10^{-5} M).
- The antagonist effect of a compound is measured by the simultaneous addition of FSK (1µM) , SRIF-14 (1 to 10 nM) and a test compound (10^{-10} M to 10^{-5} M).

The reaction medium is removed and 200 ml 0.1 N HCl is added. cAMP is measured using radioimmunoassay method (Kit FlashPlate SMP001A, New England Nuclear).

As is well known to those skilled in the art, the known and potential uses of somatostatin are varied and multitudinous. Thus, the administration of a peptide of

this invention for purposes of stimulating the somatostatin receptors can have the same effects or uses as somatostatin itself. For example, inhibiting the secretion of growth hormone, insulin, glucagon and pancreatic exocrine secretion (U.S. Patent No. 4,853,371); for treating restenosis (U.S. Patent No. 5,147,856); for treating hepatoma (U.S. Patent No. 5,411,943); for treating lung cancer (U.S. Patent No. 5,073,541); treating melanoma (U.S. Application No. 08/089,410 filed July 9, 1993); for inhibiting the accelerated growth of a solid tumor (U.S. Patent No. 5,504,069); for decreasing body weight (U.S. Application No. 08/854,941 filed May 13, 1997); for treating insulin resistance and Syndrome X (U.S. Application No. 08/854,943 filed May 13, 1997); for prolonging the survival of pancreatic cells (U.S. Patent No. 5,688,418); for treating fibrosis (PCT Application No. PCT/US97/14154); for treating hyperlipidemia (U.S. Application No. 08/855,311 filed May 13, 1997); for treating hyperamylinemia (U.S. Application No. 08/440,061 filed May 12, 1995); for treating hyperprolactinemia and prolactinomas (U.S. Application No. 08/852,221 filed May 7, 1997); Cushings Syndrome (see Clark, R.V. et al, Clin. Res. 38, p. 943A, 1990); gonadotropinoma (see Ambrosi B., et al., Acta Endocr. (Copenh.) 122, 569-576, 1990); hyperparathyroidism (see Miller, D., et al., Canad. Med. Ass. J., Vol. 145, pp. 227-228, 1991); Paget's disease (see, Palmieri, G.M.A., et al., J. of Bone and Mineral Research, 7, (Suppl. 1), p. S240 (Abs. 591), 1992); VIPoma (see Koberstein, B., et al., Z. Gastroenterology, 28, 295-301, 1990 and Christensen, C., Acta Chir. Scand. 155, 541-543, 1989); nesidioblastosis and hyperinsulinism (see Laron, Z., Israel J. Med. Sci., 26, No. 1, 1-2; 1990, Wilson, D.C., Irish J. Med. Sci., 158, No. 1, 31-32, 1989 and Micic, D., et al., Digestion, 16, Suppl. 1.70. Abs. 193, 1990); gastrinoma (see Bauer, F.E., et al., Europ. J. Pharmacol., 183, 55 1990); Zollinger-Ellison Syndrome (see Mozell, E., et al., Surg. Gynec. Obstet., 170, 476-484, 1990); hypersecretory diarrhea related to AIDS and other conditions (due to AIDS, see Cello, J.P., et al., Gastroenterology, 98, No. 5, Part 2, Suppl., A163 1990; due to elevated gastrin-releasing peptide, see Alhindawi, R., et al., Can. J. Surg., 33, 139-142, 1990; secondary to intestinal graft vs. host disease, see Bianco J.A., et al., Transplantation, 49, 1194-1195, 1990; diarrhea associated with chemotherapy, see Petrelli, N., et al., Proc. Amer. Soc. Clin. Oncol., Vol. 10, P 138, Abstr. No. 417 1991); irritable bowel syndrome (see O'Donnell, L.J.D., et al.,

Aliment. Pharmacol. Therap., Vol. 4., 177-181, 1990); pancreatitis (see Tulassay, Z., et al., Gastroenterology, 98, No. 5, Part 2, Suppl., A238, 1990); Crohn's Disease (see Fedorak, R.N., et al., Can. J. Gastroenterology, 3, No. 2, 53-57, 1989); systemic sclerosis (see Soudah, H., et al., Gastroenterology, 98, No. 5, Part 2, Suppl., A129, 1990); thyroid cancer (see Modigliani, E., et al., Ann., Endocr. (Paris), 50, 483-488, 1989); psoriasis (see Camisa, C., et al., Cleveland Clinic J. Med., 57 ,No. 1, 71-76, 1990); hypotension (see Hoeldtke, R.D., et al., Arch. Phys. Med. Rehabil., 69, 895-898, 1988 and Kooner, J.S., et al., Brit. J. Clin. Pharmacol., 28, 735P-736P, 1989); panic attacks (see Abelson, J.L., et al., Clin. Psychopharmacol., 10, 128-132, 1990); sclerodoma (see Soudah, H., et al., Clin. Res., Vol. 39, p. 303A, 1991); small bowel obstruction (see Nott, D.M., et al., Brit. J. Surg., Vol. 77, p. A691, 1990); gastroesophageal reflux (see Branch, M.S., et al., Gastroenterology, Vol. 100, No. 5, Part 2 Suppl., p. A425, 1991); duodenogastric reflux (see Hasler, W., et al., Gastroenterology, Vol. 100, No. 5, Part 2, Suppl., p. A448, 1991); Graves' Disease (see Chang, T.C., et al., Brit. Med. J., 304, p. 158, 1992); polycystic ovary disease (see Prelevic, G.M., et al., Metabolism Clinical and Experimental, 41, Suppl. 2, pp 76-79, 1992); upper gastrointestinal bleeding (see Jenkins, S.A., et al., Gut., 33, pp. 404-407, 1992 and Arrigoni, A., et al., American Journal of Gastroenterology, 87, p. 1311, (abs. 275), 1992); pancreatic pseudocysts and ascites (see Hartley, J.E., et al., J. Roy. Soc. Med., 85, pp. 107-108, 1992); leukemia (see Santini, et al., 78, (Suppl. 1), p. 429A (Abs. 1708), 1991); meningioma (see Koper, J.W., et al., J. Clin. Endocr. Metab., 74, pp. 543-547, 1992); and cancer cachexia (see Bartlett, D.L., et al., Surg. Forum., 42, pp. 14-16, 1991).

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the peptides of formula (I) in association with a pharmaceutically acceptable carrier.

In general an effective dosage for the activities of this invention, for example the treatment of acromegaly, is in the range of 0.01 to 200 mg/kg/day, preferably 0.5 to 100 mg/kg/day.

A peptide of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant),

nasal, vaginal, rectal, sublingual or topical routes of administration and can be formulated with pharmaceutically acceptable carriers to provide dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than such inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as coca butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

Further, a compound of this invention can be administered in a sustained release composition such as those described in the following patents and patent applications. U.S. Patent No. 5,672,659 teaches sustained release compositions comprising a bioactive agent and a polyester. U.S. Patent No. 5,595,760 teaches sustained release compositions comprising a bioactive agent in a gelable form. U.S. Patent No. 5,821,221, teaches polymeric sustained release compositions comprising a bioactive agent and chitosan. U.S. Application No. 08/740,778 filed November 1, 1996, teaches sustained release compositions comprising a bioactive agent and cyclodextrin. U.S. Application No. 09/015,394 filed January 29, 1998, teaches absorbable sustained release compositions of a bioactive agent. U.S. Application No. 09/121,653 filed July 23, 1998, teaches a process for making microparticles comprising a therapeutic agent such as a peptide in an oil-in-water process. U.S. Application No. 09/131,472 filed August 10, 1998, teaches complexes comprising a therapeutic agent such as a peptide and a phosphorylated polymer. U.S. Application No. 09/184,413 filed November 2, 1998, teaches complexes comprising a therapeutic agent such as a peptide and a polymer bearing a non-polymerizable lactone. The teachings of the foregoing patents and applications are incorporated herein by reference.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 0.0001 to 100 mg/kg of body weight daily are administered to humans and other animals, e.g., mammals, to obtain effective release of growth hormone.

A preferred dosage range is 0.01 to 5.0 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also, all publications, patent applications, patents, and other references mentioned herein are incorporated by reference.

CLAIMS

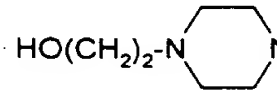
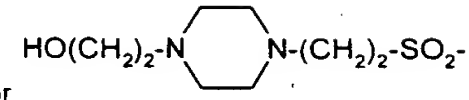
What is claimed is:

1. A peptide of the formula (I),

$$X\text{-}A^1\text{-cyclo(D-Cys-}A^3\text{-}A^4\text{-Lys-}A^6\text{-}A^7\text{)-}A^8\text{-}Y, \quad (I)$$

or a pharmaceutically acceptable salt thereof ,

wherein

X is H,  or  ;

A^1 and A^3 are each independently the D- or L-isomer of an amino acid selected from the group consisting of Phe, Tyr, Tyr(I), Trp, 3-Pal, 4-Pal, Cpa and Nal;

A^4 is L-Trp, D-Trp, L-ß-methyl-Trp or D-ß-methyl-Trp;

A^6 is -NH-$(CHR^1)_n$-CO-, where n is 2, 3, or 4;

A^7 is L- or D-Cys;

A^8 is the D- or L-isomer of an amino acid selected from the group consisting of Phe, Tyr, Tyr(I), Trp, Nal, Cpa, Val, Leu, Ile, Ser and Thr;

Y is NR^2R^3 where R^2 and R^3 are each independently H or $(C_1\text{-}C_5)$alkyl;

R^1 is selected from the group consisting H, $(C_1\text{-}C_4)$alkyl and -CH_2-aryl; wherein said aryl is an optionally substituted moiety selected from the group consisting of phenyl, 1-naphthyl, and 2-naphthyl, wherein said optionally substituted moiety is optionally substituted with one or more substituents each independently selected from the group consisting of $(C_{1\text{-}6})$alkyl, $(C_{2\text{-}6})$alkenyl, $(C_{2\text{-}6})$alkynyl, aryl, aryl$(C_{1\text{-}6})$alkyl, $(C_{1\text{-}6})$alkoxy, -$N(R^4R^5)$, -COOH, -$CON(R^4R^5)$, halo, -OH, -CN, and -NO_2;

R^4 and R^5 each is, independently for each occurrence, H or $(C_{1\text{-}3})$alkyl;

where the Cys of A^2 is bonded to the Cys of A^7 by a di-sulfide bond formed from the thiol groups of each Cys.

2. A peptide according to claim 1 wherein

A^1 is L-Phe, D-Phe, L-Cpa or D-Cpa;

A^3 is L-Tyr, L-Trp or L-3-Pal;

A^4 is D-Trp;

A^6 is β-Ala or Gaba;

A^7 is L-Cys;

A^8 is L-Thr, L-Trp, L-Leu or L-Nal; and

R^2 and R^3 are each H;

or a pharmaceutically acceptable salt thereof.

3. A peptide according to claim 2 wherein said peptide is of the formula

Cpa-cyclo(D-Cys-3-Pal-D-Trp-Lys-Gaba-Cys)-Nal-NH_2;

Cpa-cyclo(D-Cys-3-Pal-D-Trp-Lys-β-Ala-Cys)-Nal-NH_2;

Phe-cyclo(D-Cys-3-Pal-D-Trp-Lys-Gaba-Cys)-Nal-NH_2;

Phe-cyclo(D-Cys-Tyr-D-Trp-Lys-Gaba-Cys)-Nal-NH_2;

Phe-cyclo(D-Cys-Trp-D-Trp-Lys-Gaba-Cys)-Nal-NH_2;

Phe-cyclo(D-Cys-Tyr-D-Trp-Lys-Gaba-Cys)-Trp-NH_2;

D-Phe-cyclo(D-Cys-Tyr-D-Trp-Lys-Gaba-Cys)-Nal-NH_2;

D-Phe-cyclo(D-Cys-Tyr-D-Trp-Lys-Gaba-Cys)-Leu-NH_2; or

Phe-cyclo-(D-Cys-Tyr-D-Trp-Lys-Gaba-Cys)-Thr-NH_2;

or a pharmaceutically acceptable salt thereof.

4. A peptide according to claim 3 wherein said peptide is of the formula

Cpa-cyclo(D-Cys-3-Pal-D-Trp-Lys-Gaba-Cys)-Nal-NH_2; or

Cpa-cyclo(D-Cys-3-Pal-D-Trp-Lys-β-Ala-Cys)-Nal-NH_2;

or a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition useful for eliciting a somatostatin agonist response in a human or other animal which comprises an effective amount of a peptide of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

6. A method of eliciting a somatostatin agonist response in a human or other animal in need thereof, which comprises administering an effective amount of a peptide of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof to the human or other animal.

7. A method of selectively binding a somatostatin subtype receptor type 5 in a human or other animal, which comprises administering an effective amount of a peptide of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof to the human or other animal.

8. A method of treating a disease or condition in a human or other animal in need thereof, which comprises administering a peptide of formula (I) or a pharmaceutically acceptable salt thereof to said human or other animal, wherein said disease or condition is selected from the group consisting of Cushings Syndrome, gonadotropinoma, hyperparathyroidism, Paget's disease, VIPoma, nesidioblastosis, hyperinsulinism, gastrinoma, Zollinger-Ellison Syndrome, hypersecretory diarrhea related to AIDS and other conditions, irritable bowel syndrome, pancreatitis, Crohn's Disease, systemic sclerosis, thyroid cancer, psoriasis, hypotension, panic attacks, sclerodoma, small bowel obstruction, gastroesophageal reflux, duodenogastric reflux, Graves' Disease, polycystic ovary disease, upper gastrointestinal bleeding, pancreatic pseudocysts, pancreatic ascites, leukemia, meningioma, cancer cachexia, acromegaly, restenosis, hepatoma, lung cancer, melanoma, inhibiting the accelerated growth of a solid tumor, decreasing body weight, treating insulin resistance, Syndrome X, prolonging the survival of pancreatic cells, fibrosis, hyperlipidemia, hyperamylinemia, hyperprolactinemia and prolactinemia.

9. A method of inhibiting the secretion of growth hormone, insulin, glucagon or pancreatic exocrine secretion in a human or other animal in need thereof, which comprises administering a peptide of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof to said human or other animal.

10. A method of imaging cells containing somatostatin receptors *in vivo* in a human or other animal, which comprises administering a peptide of formula (I) according to claim 1, provided that at least one of A^1, A^3 or A^8 is Tyr(I), or a pharmaceutically acceptable salt thereof to said human or other animal.

11. A method of imaging cells containing somatostatin receptors *in vitro*, which comprises administering a peptide of formula (I) according to claim 1, provided that at least one of A^1, A^3 or A^8 is Tyr(I), or a pharmaceutically acceptable salt thereof to said human or other animal.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/17401

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/655 C07K7/02 A61K38/31 A61P5/02 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 98 24807 A (BIOMEASURE INC ;MORGAN BARRY (US); MURPHY WILLIAM (US); ADMINISTRA) 11 June 1998 (1998-06-11) page 22, line 1-4; claims page 24	1,2,5-11 3,4
Y	EP 0 505 680 A (BIOSIGNAL KUTATO FEJLESZTOE) 30 September 1992 (1992-09-30) page 7, line 35; example 14	3,4

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 November 2000	10/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cervigni, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 00/17401

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HOCART S J ET AL: "POTENT ANTAGONISTS OF SOMATOSTATIN: SYNTHESIS AND BIOLOGY" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 41, no. 7, 26 March 1998 (1998-03-26), pages 1146-1154, XP000749590 ISSN: 0022-2623 table 1 ---	
A	COY D H ET AL: "SOMATOSTATIN RECEPTOR ANTAGONISTS BASED ON A MIXED NEUROMEDIN B ANTAGONIST/SOMATOSTATIN AGONIST" PROCEEDINGS OF THE AMERICAN PEPTIDE SYMPOSIUM, 1999, XP000917964 table 1 ---	
A	US 4 603 120 A (KAMBER BRUNO) 29 July 1986 (1986-07-29) abstract ---	
A	WO 95 04752 A (BIOMEASURE INC) 16 February 1995 (1995-02-16) ---	
A	RAYNOR K ET AL: "CHARACTERIZATION OF CLONED SOMATOSTATIN RECEPTORS SSTR4 AND SSTR5" MOLECULAR PHARMACOLOGY,US,BALTIMORE, MD, vol. 44, no. 2, 1 August 1993 (1993-08-01), pages 385-392, XP000644418 ISSN: 0026-895X ---	
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A	WO 98 51331 A (SOD CONSEILS RECH APPLIC ;CAWTHORNE MICHAEL ANTHONY (GB); SENNITT) 19 November 1998 (1998-11-19) -----	

INTERNATIONAL SEARCH REPORT

Int[redacted]al Application No
PCT/US 00/17401

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/17401

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 0981363 A	01-03-2000

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

TSAO, Y. Rocky
FISH & RICHARDSON P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
ETATS-UNIS D'AMERIQUE

2001

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	26.09.2001
Applicant's or agent's file reference 00537-191WO1	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/17401	23/06/2000	25/06/1999

Applicant
SOCIETE DE CONSEILS DE RECHERCHES ET D'APPL..et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hingel, W Tel.+49 89 2399-8717

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
00537-191WO1		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/17401	23/06/2000	25/06/1999
International Patent Classification (IPC) or national classification and IPC C07K14/655		
Applicant SOCIETE DE CONSEILS DE RECHERCHES ET D'APPL..et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25/01/2001	26.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Rojo Romeo, E Telephone No. +49 89 2399 7321

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/17401

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-17 as originally filed

Claims, No.:

1-11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-11 (partially).

because:

☒ the said international application, or the said claims Nos. 1-11 (partially) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-11 (partially).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	6-11 (see separate sheet)

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I

Basis of this report

Since the Applicant failed to reply to the Written Opinion, the present IPER is based on said Written Opinion.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The present set of claims is directed to an extremely large number of possible compounds. Consequently, the entire scope of claim 1 cannot be construed without an immense burden of work and the examination is limited to the two compounds given in the examples. any other subject-matter is therefore, disregarded.

Re Item IV

Lack of unity of invention

The present application concerns cyclic peptides having a somatostatin agonist activity. The common inventive concept linking the present set of claims is the general formula I, i.e. substituted cyclic peptides having somatostatin agonist activity. As mentioned in the present application (see e.g. page 4) and in prior art (see D3-D6), cyclic hexa- and octa-peptides have been synthesized which possess the whole spectrum of effects of somatostatin. Moreover, some of the specific claimed compounds are disclosed in e.g. D1. In view of the prior art, the common concept linking the claimed compounds is not inventive and the problem of the present application can be redefined as the provision of additional peptides having somatostatin activity.
Consequently, each and every single compound may be considered, in the regional phase as an independent invention.

The Applicant's attention is drawn to the fact that each of the two claimed compounds may be considered to define an independent invention in the regional phase.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following comments are made as far as the claims concern the two compounds for which the synthesis is described in the examples and which are claimed in claim 4.

Reference is made to the following documents cited in the International Search Report:

D1: WO 98 24807 A (BIOMEASURE INC ;MORGAN BARRY (US); MURPHY WILLIAM (US); ADMINISTRA) 11 June 1998 (1998-06-11)

D2: EP-A-0 505 680 (BIOSIGNAL KUTATO FEJLESZTOE) 30 September 1992 (1992-09-30)

D3: WO 98 50063 A (CEDARS SINAI MEDICAL CENTER ;MELMED SHLOMO (US); SHIMON ILAN (US);) 12 November 1998 (1998-11-12)

D4: WO 98 51332 A (SOD CONSEILS RECH APPLIC ;CAWTHORNE MICHAEL ANTHONY (GB); SENNITT) 19 November 1998 (1998-11-19)

D5: WO 98 51330 A (SOD CONSEILS RECH APPLIC ;CAWTHORNE MICHAEL ANTHONY (GB); SENNITT) 19 November 1998 (1998-11-19)

D6: WO 98 51331 A (SOD CONSEILS RECH APPLIC ;CAWTHORNE MICHAEL ANTHONY (GB); SENNITT) 19 November 1998 (1998-11-19)

1. Novelty (Art. 33(2) PCT)

None of the documents cited in the International Search Report discloses the claimed subject-matter. The current set of claims is thus considered novel over these documents as far as they concern the two compounds mentioned above.

The Applicant's attention is drawn to the fact that many of the compounds claimed in D1 fall under the scope of claim 1. Thus the broad claim as it stands would not be novel over prior art.

2. Inventive step (Art. 33(3) PCT)

D1 or D2 can be considered as closest prior art since these documents disclose somatostatin homologs. The problem underlying the present application is the provision of somatostatin homologs with somatostatin agonist activity. The solution provided by the present application is the provision of the two compounds of claim 4. There was no hint in the prior art for the synthesis of these specific two compounds and that these compounds may have somatostatin agonist activity. Thus, inventive activity could be acknowledged for these two specific compounds, given that the data can be provided that these compounds indeed have the claimed technical effects (i.e. somatostatin agonist). Moreover, as mentioned at page 1 of the present application somatostatin analogs (i.e. having agonist activity) were also known from prior art. The present application fails to show that the two claimed compounds have a technical

advantage over the somatostatin analogs already known (see D3-D6). In the absence of such data, inventive activity cannot be acknowledged for the present set of claims.

In addition, the Applicant's attention is drawn to the fact that the use of somatostatin analogs having a Tyr at position A1 for imaging was known from prior art (see e.g. D1, page 24). Consequently, the skilled person would use any other somatostatin analog having this technical characteristic for this purpose. Thus claims 10 and 11 lack inventive activity.

Consequently, claims 1-11 lack inventive step.

3. Industrial applicability (Art. 33(4) PCT)

For the assessment of the present claims 6-11 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

1. Clarity (Art. 6 PCT)

1.1 The Applicant's attention is drawn to the fact that the intention of use does not limit the scope of a claim which is directed to a composition. The claim must be interpreted as being directed to a composition per se regardless of its use. No unified criteria exist in the PCT as far as first medical use is concerned. The EPO, for instance, will allow claims in a form such as:"substance or composition X", followed by the indication of use ("for use as a medicament"). Thus, claim 5 is read as being directed to a composition comprising either of the two claimed peptides.

1.2 Concerning claims 5-7, in the absence of data concerning the use of the claimed compounds, the term "effective amount" is unclear.

2. Support by specification (Art. 6 PCT), in combination with Art. 5 PCT (complete and

enabling disclosure)

2.1 No data is provided concerning the activity of the two claimed compounds (somatostatin agonist activity, selective binding to somatostatin subtype receptor type 5). Thus, the assumption that these compounds have somatostatin agonist activity is speculative. Concerning this, it is noteworthy to mention that the present specification recommends to test the claimed compounds for agonist or antagonist activity (see page 13)! An objection for lack of support thus arises.

2.1 Similarly, the uses of the two claimed compounds in medical treatment are based on speculations derived from the uses of somatostatin itself but without any experimental proof and are therefore also the subject of an objection for lack of support by the specification (claims 6-9).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
00537-191W01		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/17401	23/06/2000	25/06/1999
Applicant		
SOCIETE DE CONSEILS DE RECHERCHES ET D'APPL..		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   SOMATOSTATIN AGONISTS

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. --

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/17401

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/655 C07K7/02 A61K38/31 A61P5/02 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 24807 A (BIOMEASURE INC ;MORGAN BARRY (US); MURPHY WILLIAM (US); ADMINISTRA) 11 June 1998 (1998-06-11)	1,2,5-11
Y	page 22, line 1-4; claims page 24	3,4
Y	EP 0 505 680 A (BIOSIGNAL KUTATO FEJLESZTOE) 30 September 1992 (1992-09-30) page 7, line 35; example 14	3,4

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 November 2000	10/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cervigni, S

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	HOCART S J ET AL: "POTENT ANTAGONISTS OF SOMATOSTATIN: SYNTHESIS AND BIOLOGY" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 41, no. 7, 26 March 1998 (1998-03-26), pages 1146-1154, XP000749590 ISSN: 0022-2623 table 1	
A	COY D H ET AL: "SOMATOSTATIN RECEPTOR ANTAGONISTS BASED ON A MIXED NEUROMEDIN B ANTAGONIST/SOMATOSTATIN AGONIST" PROCEEDINGS OF THE AMERICAN PEPTIDE SYMPOSIUM, 1999, XP000917964 table 1	
A	US 4 603 120 A (KAMBER BRUNO) 29 July 1986 (1986-07-29) abstract	
A	WO 95 04752 A (BIOMEASURE INC) 16 February 1995 (1995-02-16)	
A	RAYNOR K ET AL: "CHARACTERIZATION OF CLONED SOMATOSTATIN RECEPTORS SSTR4 AND SSTR5" MOLECULAR PHARMACOLOGY,US,BALTIMORE, MD, vol. 44, no. 2, 1 August 1993 (1993-08-01), pages 385-392, XP000644418 ISSN: 0026-895X	
A	WO 98 50063 A (CEDARS SINAI MEDICAL CENTER ;MELMED SHLOMO (US); SHIMON ILAN (US);) 12 November 1998 (1998-11-12)	
A	WO 98 51332 A (SOD CONSEILS RECH APPLIC ;CAWTHORNE MICHAEL ANTHONY (GB); SENNITT) 19 November 1998 (1998-11-19)	
A	WO 98 51330 A (SOD CONSEILS RECH APPLIC ;CAWTHORNE MICHAEL ANTHONY (GB); SENNITT) 19 November 1998 (1998-11-19)	
A	WO 98 51331 A (SOD CONSEILS RECH APPLIC ;CAWTHORNE MICHAEL ANTHONY (GB); SENNITT) 19 November 1998 (1998-11-19)	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/17401

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9824807 A	11-06-1998	AU 7624898 A	29-06-1998
		BR 9714376 A	21-03-2000
		EP 0956296 A	17-11-1999
		PL 334089 A	31-01-2000
EP 0505680 A	30-09-1992	HU 60752 A	28-10-1992
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		IE 54494 B	25-10-1989
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		EP 0788509 A	13-08-1997
		FI 960584 A	08-02-1996
		HU 73491 A	28-08-1996
		JP 9501177 T	04-02-1997
		LT 96025 A,B	25-07-1996
		LV 11549 A	20-10-1996
		LV 11549 B	20-04-1997
		NZ 271238 A	24-10-1997
		PL 312989 A	27-05-1996
		RU 2133252 C	20-07-1999
		SI 9420051 A	31-12-1996
		SK 15096 A	03-07-1996
		US 5552520 A	03-09-1996
		ZA 9405966 A	26-06-1995
WO 9850063 A	12-11-1998	US 5972893 A	26-10-1999
		EP 0979098 A	16-02-2000
WO 9851332 A	19-11-1998	AU 8019898 A	08-12-1998
		EP 0980253 A	23-02-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/17401

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9851330 A	19-11-1998	AU 8019798 A	08-12-1998
		EP 0981364 A	01-03-2000
WO 9851331 A	19-11-1998	AU 7655098 A	08-12-1998
		EP 0981363 A	01-03-2000

'ATENT COOPERATION TR TY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 March 2001 (08.03.01)	
International application No. PCT/US00/17401	**Applicant's or agent's file reference** 00537-191WO1
International filing date (day/month/year) 23 June 2000 (23.06.00)	**Priority date** (day/month/year) 25 June 1999 (25.06.99)
Applicant MORGAN, Barry, A. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

25 January 2001 (25.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Claudio Borton
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

US0017401

-continued

1 5

What we claim is:

1. A heptapeptide or octapeptide amide derivative selected from the group consisting of

β-aspartyl-(indolinyl)-

Cys—Tyr—D—Trp—Lys—Val—Cys—Thr—NH_2,

D—Phg—Cys—Tyr—D—Trp—Lys—Val—Cys—Thr—NH_2,

D—Phe—Cys—Tyr—D—Trp—Lys—Cys—Thr—NH_2,

D—Phe—

—Cys—Tyr—β—Asp(indolinyl)—Lys—Leu—Cys—Thr—NH_2,

D—Phe—Tyr—Tyr—Aa—Lys—Val—Phe—Trp—NH_2,

Ac—Sar—Ala—Tyr—Tyr—Aa—Lys—Val—Phe—Trp—NH_2,

Pop—Tyr—Tyr—Aa—Lys—Val—Phe—Trp—NH_2,

Aa—Cys(Acm)—Tyr—D—Trp—

—Lys—Val—Cys(Acm)—Trp—NH_2,

β—Asp(NH—Ph)—

—Cys—Tyr—D—Trp—Lys—Val—Cys—Thr—NH_2,

Tic—Cys—Tyr—D—Trp—Lys—Val—Cys—Thr—NH_2,

D—Phe—

—Cys—Tyr—D—Trp—Lys(Tfa)—Val—Cys—Thr—NH_2,

D—Phe—

—Cys—Tyr—D—Trp—Lys—β—Ala—Cys—Thr—NH_2,

D—Phe—Cys—Tyr—D—Trp—Lys—Pro—Cys—Thr—NH_2,

Ac—Sar—Tyr—Tyr—Aa—Lys—Val—Phe—Trp—NH_2,

D—Phe—Ala—Tyr—Aa—Lys—Val—Phe—Trp—NH_2,

D—Phe—Cys—Tyr—Aa—Lys—Val—Cys—Trp—NH_2,

D-2-naphthyl-alanyl-

Cys—Tyr—Aa—Lys—Val—Cys—Trp—NH_2,

Aa—Cys—Tyr—D—Trp—Lys—Val—Cys—Trp—NH_2,

D—Phe—Cys—Tyr—Asu—Lys—Val—Cys—Thr—NH_2,

D—Phe—

—Cys—Tyr—β—Asp(indolinyl)—Lys—Val—Cys—Thr—NH_2,

-continued

Pop—Cys—Tyr—D—Trp—Lys—Val—Cys—Thr—NH_2,

Mab—Cys—Phe—D—Trp—Lys—Val—Cys—Trp—NH_2,

D-2-naphthyl-alanyl-

Cys—Tyr—D—Trp—Lys—Val—Cys—Thr—NH_2,

D—Phe—Cys—Tyr—Aa—Lys—Val—Trp—NH_2,

D-2-naphthyl-alanyl-

Cys—Tyr—Aa—Lys—Val—Cys—Thr—NH_2,

and

Ac—Sar—Ala—Tyr—Aa—Lys—Val—Cys—Trp—NH_2.

2. A pharmaceutical composition which comprises as active ingredient a heptapeptide or octapeptide amide derivative as defined in claim **1** or a pharmaceutically acceptable acid addition salt thereof in admixture with carriers and/or additives commonly used in the pharmaceutical industry.

3. A method for treating mammals, including man, suffering from tumors or from the excessive secretion of insulin, glucagon or growth hormone, consisting of administering a therapeutically effective amount of a heptapeptide or octapeptide amide derivative as defined in claim **1**, or a pharmaceutically acceptable acid addition salt thereof.

4. The method of claim **3**, wherein the heptapeptide amide derivative is

D—Phe—Cys—Tyr—D—Trp—Lys—Cys—Thr—NH_2.

5. The method of claim **3**, wherein the octapeptide amide derivative is

β-aspartyl-(indolinyl)-

Cys—Tyr—D—Trp—Lys—Val—Cys—Thr—NH_2.

6. The composition of claim **2**, wherein the octapeptide amide derivative is

D—Phe—Cys—Tyr—D—Trp—Lys—Cys—Thr—NH_2.

7. The composition of claim **2**, wherein the octapeptide amide derivative is

β-aspartyl-(indolinyl)-

INTERNATIO L SEARCH REPORT

Inter[redacted]al Application No
PCT/US 00/17401

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/655 C07K7/02 A61K38/31 A61P5/02 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 24807 A (BIOMEASURE INC ;MORGAN BARRY (US); MURPHY WILLIAM (US); ADMINISTRA) 11 June 1998 (1998-06-11)	1,2,5-11
Y	page 22, line 1-4; claims page 24	3,4
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
3 November 2000	10/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cervigni, S

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	HOCART S J ET AL: "POTENT ANTAGONISTS OF SOMATOSTATIN: SYNTHESIS AND BIOLOGY" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 41, no. 7, 26 March 1998 (1998-03-26), pages 1146-1154, XP000749590 ISSN: 0022-2623 table 1 ---	
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